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Steroids

Facile synthesis of 17-formyl steroids via palladium-catalyzed homogeneous carbonylation reaction

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Abstract

17-Formyl-androst-16-ene and its analogues were synthesized from the corresponding 17-iodo-16-ene derivatives in palladium-catalyzed formylation reaction using tributyltin hydride as hydrogen source under mild reaction conditions. The formation of androst-16-ene and its isomerization products, as well as that of analogous steroidal olefins as side-products, was found to be dependant on the reaction conditions. The formylation reaction tolerates various functional groups on the A and B rings of the steroids. © 2002 Elsevier Science Inc. All rights reserved.

Keywords: Steroids; 17-Iodo-16-enes; 17-Formyl-steroids; Tributyltin hydride; Palladium catalysts; Carbonylation

1. Introduction

The homogeneous catalytic functionalization of biologically important skeletons, among them steroids, is an efficient method for the synthesis of new derivatives. The formyl group (especially at the distinguished position-17 of an androstane-skeleton) may serve as a functionality for further build-up of a steroid. Although steroidal formyl derivatives, which possess formyl group attached to the D-ring, are available via homogeneous hydroformylation of steroidal alkenes, in most cases rather complex mixture of formyl stereoisomers has been obtained [1].

The palladium-catalyzed carbon monoxide-based formylation reaction [2] involves either the use of CO/H_2 mixture [3], sodium formate [4] or that of poly(methylhydrosiloxane) [5] as hydrogen source and aryl or allyl halides as substrates. A low-pressure versatile formylation reaction has also been developed for the conversion of aryl, benzyl, and vinyl halides using tributylstannane as a hydrogen donor and $Pd(PPh_3)_4$ as catalyst [6].

In the present paper, we report on the efficient novel synthesis of steroids possessing 17-formyl-16-ene moiety in palladium-catalyzed carbonylation of 'iodo-vinyl' steroids bearing 17-iodo-16-ene functionality. Our method based on the application of simple starting materials like easily accessible iodoalkenes [7] provides a novel approach for the synthesis of formyl steroids. Furthermore, the undesired side-reactions and the effect of some of the reaction parameters on yields will also be discussed.

2. Experimental

$Pd(OAc)_2$, PPh_3, dppp, dppb, and tributyltin hydride were commercial products. Commercial DMF and Et_3N were used without further purification. Toluene was dried over sodium and distilled under argon. Steroidal 17-iodo-16-enes were synthesized according to an analogous method by using the 17-keto derivatives. They were converted into hydrazones, those were treated with iodine in the presence of a base resulting in the formation of the corresponding 17-iodo-16-enes, **1**–**5** [7–10].

The ^1H and ^{13}C NMR spectra were recorded on a VARIAN INOVA 400 spectrometer at 400 and 100.58 MHz, respectively. The chemical shifts are given as δ values (ppm), with tetramethylsilane as the internal standard. GLC analyses were carried out with a HP-5890/II gas chromatograph using a 15 m HP-5 column (temperature program: initial temperature: 200 °C ((2 min), rate: 10 °C/min, final temperature: 300 °C, flow rate: 0.976 ml/min (constant flow))).

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2.1. General procedure for the synthesis of steroidal formyl derivatives

A mixture of an 'iodo-vinyl' derivative (1 mmol), palladium(II) acetate (11.2 mg, 0.05 mmol), and triphenylphosphine (26.2 mg, 0.1 mmol) (or 1,4-bis(diphenylphosphino)-butane (dppb), 1,3-bis(diphenylphosphino)-propane (dppp) 0.05 mmol)) were dissolved in 14 ml toluene under argon. The atmosphere was changed to carbon monoxide (1 bar), then tributyltin hydride (0.32 ml, 1.2 mmol) dissolved in 3 ml toluene was added dropwise to the reaction mixture at 50 °C in 2 h. The reaction was conducted for an additional 6 h. (The composition of the reaction mixture was checked by TLC and determined by GC-MS.) The solvent was evaporated to dryness, and the rest was dissolved in 10 ml of chloroform. Potassium fluoride (0.2 g) dissolved in 10 ml water was added and stirred vigorously for 10 h. The organic layer was separated, dried on sodium sulfate and evaporated. The chromatography (silicagel, toluene/methanol = 4/1) resulted in the formyl-products in 50–75% isolated yields.

2.2. Analytical and spectroscopic data of compounds

2.2.1. 17-Formyl-androst-16-ene (**6**)

^{1}H NMR ($CDCl_3$, 400 MHz): 9.68 (s, 1H, CHO); 6.76 (dd, 1.7 Hz, 3.4 Hz, 1H, 16-CH); 2.34 (ddd, 3.4 Hz, 6.4 Hz, 17.5 Hz, 1H, 15-CH_aH$_b$); 2.04 (ddd, 1.7 Hz, 11.9 Hz, 17.5 Hz, 1H, 15-CH$_a$$H_b$); 0.88 (s, 3H, 18-$CH_3$); 0.80 (s, 3H, 19-$CH_3$); ^{13}C NMR (100.58 MHz, $CDCl_3$): 190.1 (CHO); 157.2 (17-C); 153.1 (16-C); 56.6; 55.4; 47.5; 47.2; 38.5; 36.5; 34.4; 33.8; 32.7; 32.1; 29.1; 28.9; 26.8; 22.0; 20.6; 13.6 (18-CH_3); 12.2 (19-CH_3); MS (*m*/*z*/rel. int.): 286/62 (M^+); 271/40 (M^+–CH_3); 257/90 (M^+–CHO), 189/100. Analysis calculated for $C_{20}H_{30}O$ (M = 286.46): C, 83.86; H, 10.56; Found: C, 83.58; H, 10.28.

2.2.2. 17-Formyl-4-aza-4-methyl-androst-16-en-3-one (**7**)

^{1}H NMR ($CDCl_3$, 400 MHz): 9.69 (s, 1H, CHO); 6.77 (dd, 1.6 Hz, 3.2 Hz, 1H, 16-CH); 3.03 (m, 1H, 5-CH); 2.91 (s, 3H, N-CH_3); 1.2–2.5 (m, 17H, ring protons); 1.05 (s, 3H, 18-CH_3); 0.89 (s, 3H, 19-CH_3). MS (*m*/*z*/rel. int.): 315/66 (M^+); 300/12 (M^+–CH_3); 286/22 (M^+–CHO); 70/100. Analysis calculated for $C_{20}H_{29}NO_2$ (M = 315.46): C, 76.15; H, 9.27; N, 4.44; Found: C, 75.90; H, 9.02; N, 4.26.

2.2.3. 17-Formyl-4-aza-androst-16-en-3-one (**8**)

^{1}H NMR ($CDCl_3$, 400 MHz): 9.60 (s, 1H, CHO); 6.70 (dd, 1.7 Hz, 3.4 Hz, 1H, 16-CH); 6.4 (brs, 1H, NH); 3.06 (dd, 4.4 Hz, 11.6 Hz, 1H, 5-CH); 2.40 (m, 2H, 2-CH_2); 2.10 (ddd, 1H, 15-CH_aH$_b$); 1.95 (ddd, 1H, 15-CH_bH$_b$); 1.80–0.80 (13H; skeleton protons); 0.99 (s, 3H, 18-CH_3); 0.94 (s, 3H, 19-CH_3); MS (*m*/*z*/rel. int.): 301/60 (M^+); 286/38 (M^+–CH_3); 272/51 (M^+–CHO); 56/100. Analysis calculated for $C_{19}H_{27}NO_2$ (M = 301.43): C, 75.71; H, 9.03; N, 4.65; Found: C, 75.49; H, 9.31; N, 4.33.

2.2.4. 17-Formyl-3-methoxy-estra-1,3,5(10),16-tetraene (**9**)

^{1}H NMR ($CDCl_3$, 400 MHz): 9.73 (s, 1H, CHO); 6.70 (d, 8.4 Hz, 1H, 1-CH); 7.19 (dd, 3.2 Hz, 8.4 Hz, 1H, 2-CH); 6.81 (dd, 2.0 Hz, 3.6 Hz, 1H, 16-CH); 6.62 (d, 3.2 Hz, 1H, 4-CH); 3.76 (s, 3H, OCH_3); 2.86 (m, 2H, 6-CH_2); 2.3 (m, 4H; skeleton protons); 2.05 (ddd, 1H, 15-H_aH$_b$); 1.9 (m, 1H, 15-H$_a$$H_b$); 1.6 (m, 4H; skeleton protons); 1.4 (m, 1H; skeleton proton); 0.96 (s, 3H, 18-CH_3); MS (*m*/*z*/rel. int.): 296/100 (M^+); 173/50; 160/62. Analysis calculated for $C_{20}H_{24}O_2$ (M = 296.41): C, 81.04; H, 8.16; Found: C, 80.83; H, 8.40.

2.2.5. 17-Formyl-6b-hydroxy-3a,5a-cycloandrost-16-ene (**10**)

^{1}H NMR ($CDCl_3$, 400 MHz): 9.73 (s, 1H, CHO); 6.80 (dd, 2.0 Hz, 3.4 Hz, 1H, 16-CH); 4.30 (m, 1H, 6-H); 3.3 (t, 1H, 6-OH); 2.20–0.80 (16H; skeleton protons); 1.10 (s, 3H, 18-CH_3); 0.97 (s, 3H, 19-CH_3); 0.54 (t, 6.5 Hz, 1H, 3-CH); 0.30 (dd, 6 Hz, 11 Hz, 1H, 4-H$_a$); MS (*m*/*z*/rel. int.): 282/55 (M^+–H_2O); 267/30 ((M^+–H_2O–CH_3); 145/65; 121/100. Analysis calculated for $C_{20}H_{28}O_2$ (M = 300.44): C, 79.96; H, 9.39; Found: C, 79.71; H, 9.15.

2.3. MS data for the side-products (m/z/rel. int.)

2.3.1. Androst-16-ene (**1a**)

258/46 (M^+); 243/100 (M^+–CH_3); 148/72; 94/86; retention time (RT, under GC conditions specified above): 9.7 min.

2.3.2. Androst-15-ene (**1b**)

258/69 (M^+); 243/45 (M^+–CH_3); 148/70; 94/100; RT: 10.8 min.

2.3.3. 4-Aza-4-methyl-androst-16-en-3-one (**2a**)

287/80 (M^+); 272/45 (M^+–CH_3); 124/50; 70/100; RT: 14.4 min.

2.3.4. 4-Aza-4-methyl-androst-15-en-3-one (**2b**)

287/52 (M^+); 272/5 (M^+–CH_3); 112/100; 70/41; RT: 14.9 min.

2.3.5. 4-Aza-androst-16-en-3-one (**3a**)

273/82 (M^+); 258/100 (M^+–CH_3); 147/70; 91/96; RT: 14.3 min.

2.3.6. 4-Aza-androst-15-en-3-one (**3b**)

273/100 (M^+); 258/53 (M^+–CH_3); 180/55; 98/76; RT: 14.9 min.

2.3.7. 3-Methoxy-estra-1,3,5(10),16-tetraene (**4a**)

268/100 (M^+); 253/20 (M^+–CH_3); 173/56; 147/40; RT: 15.2 min.

*2.3.8. 3-Methoxy-estra-1,3,5(10),15-tetraene (**4b**)*

268/42 (M^+); 253/3 (M^+–CH_3); 173/22; 147/100; RT: 16.1 min.

*2.3.9. 6β-Hydroxy-3α,5α-cycloandrost-16-ene (**5a**)*

254/45 (M^+–H_2O); 239/41 (M^+–H_2O–CH_3); 145/100; 133/84; RT: 10.1 min.

*2.3.10. 6β-Hydroxy-3α,5α-cycloandrost-15-ene (**5b**)*

254/42 (M^+–H_2O); 239/100 (M^+–H_2O–CH_3); 145/10; 133/21; RT: 10.6 min.

3. Results and discussion

17-Iodo-androst-16-ene (**1**), 17-iodo-4-aza-4-methyl-androst-16-en-3-one (**2**), 17-iodo-4-aza-androst-16-en-3-one (**3**), 17-iodo-3-methoxy-estra-1,3,5(10),16-tetraene (**4**), and 17-iodo-6β-hydroxy-3α,5α-cycloandrost-16-ene (**5**) (Fig. 1) were reacted with carbon monoxide and tributyltin hydride in toluene in the presence of palladium–phosphine 'in situ' catalysts. (The 'in situ' formation of highly active Pd(0) catalyst with mono and bidentate phosphines has been published before [11].) The corresponding 17-formyl-16-ene derivatives (17-formyl-androst-16-ene (**6**), 17-formyl-4-aza-4-methyl-androst-16-en-3-one (**7**), 17-formyl-4-aza-androst-16-en-3-one (**8**), 17-formyl-3-methoxy-estra-1,3,5(10),16-tetraene (**9**), 17-formyl-6β-hydroxy-3α,5α-cycloandrost-16-ene (**10**)) were synthesized in moderate to good yields, which depend strongly on the reaction conditions (Fig. 2, Table 1).

The formation of the two types of products (unsaturated formyl and olefinic derivatives) can be explained by the following two different reaction mechanisms. The palladium–alkenyl intermediate which is formed in the oxidative addition of the 'iodo-vinyl' substrate onto the 'in situ' formed palladium(0) species may react in two pathways (Fig. 3). (i) It may insert CO and the acyl intermediate formed this way undergoes hydrostannolysis yielding the target compounds, **6–10**. (ii) The direct reaction of palladium–alkenyl intermediate with tributyltin hydride results in the formation of the 16-ene and via their isomerization the 15-ene olefinic side products (androst-16-ene (**1a**), 4-aza-4-methyl-androst-16-en-3-one (**2a**), 4-aza-androst-16-en-3-one (**3a**), 3-methoxy-estra-1,3,5(10),16-tetraene (**4a**), 6β-hydroxy-3α,5α-cycloandrost-16-ene (**5a**) and androst-15-ene (**1b**), 4-aza-4-methyl-androst-15-en-3-one (**2b**), 4-aza-androst-15-en-3-one (**3b**), 3-methoxy-estra-1,3,5(10),15-tetraene (**4b**), 6β-hydroxy-3α,5α-cycloandrost-15-ene (**5b**), respectively). The formation of 16-ene derivatives might occur also via radical dehalogenation. The olefinic side-products possessing 16- and 15-ene functionalities were not isolated as pure substances from the reaction mixtures. They were identified after base-line separation by GC–MS (see analytical data) and by using the corresponding reference compounds for GC and TLC. The reference 16-ene compounds (**1a–5a**) of known structure were synthesized from the corresponding iodoalkenes by the method of Cox and Turner [7] and Barton et al. [8]. The formation of 15-ene side-products (**1b–5b**) upon isomerization of 16-ene compounds (**1a–5a**) has also been observed for estradiol [12]. The analogous dehydratation of the corresponding 17-hydroxy steroids also served as an applicable procedure in our case for the synthesis of the mixture of 16- and 15-ene derivatives [12,13]. The 15-ene byproducts show characteristic olefinic signals in the ^{1}H NMR of the crude reacion mixtures. The broad singlets at around 6.6 ppm (6.60, 6.58, 6.60, 6.60, and 6.63 ppm for **1b**, **2b**, **3b**, **4b**, and **5b**, respectively) are characteristic for the 15-ene isomerization compounds. (In addition to GC–MS analysis, the ^{1}H NMR, based on the integrals of the olefinic protons, also served as a useful tool for the quantitative analysis of the product distribution.)

It turned out, that both the conversion and the chemoselectivity of the reaction is mainly determined by two factors: (i) the rate of the addition of tributyltin hydride solution and (ii) the type of the bidentate phosphine. Upon slow addition of tributyltin hydride to the reaction mixture (see general procedure) hydrogenolysis takes place to a small extent (15–30%) and the appropriate 17-formyl-derivatives (**6–10**) are the only formyl-products. However, when the tributyltin hydride solution was added within 10 min, the amount of the hydrodehalogenation products (**1a–5a** and **1b–5b)** predominates (55–65% of the products) over that of **6–10**, especially in case of **3** and **5**

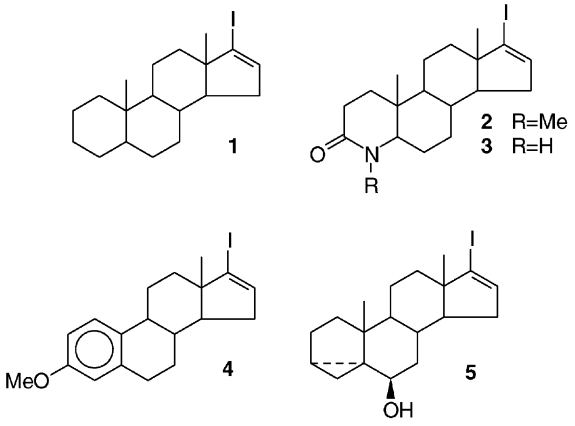

Fig. 1. Steroidal 17-iodo-16-ene derivatives (**1–5**) used as substrates.

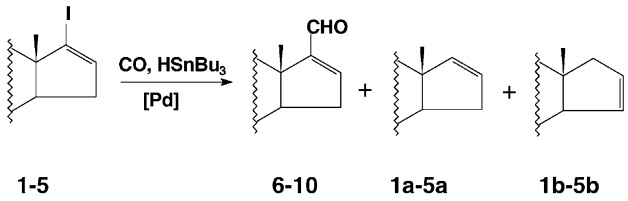

Fig. 2. Products formed in palladium-catalyzed reactions of 17-iodo-16-enes (**1–5**).

Table 1
Formylation of 17-iodo-16-enes (**1**–**5**) in the presence of $Pd(OAc)_2$ + phosphine catalysts[a]

Run	Substrate	Method[b]	Phosphine	Conversion[c] (%)	Product distribution[c] (%)		
					17-CHO, **6**–**10** (isolated yields in brackets)	**1a**–**5a**	**1b**–**5b**
1	**1**	A	PPh_3	83	45	23	32
2	**1**	B	PPh_3	89	71 (52)	14	15
3	**1**	B	dppp	90	77 (58)	13	10
4	**1**	A	dppb	60	43	36	21
5	**1**	B	dppb	97	79 (70)	15	6
6	**1**	B	PPh_3 + dppb	43	69 (53)	4	27
7	**1**	B	dpdcf	35	68 (52)	14	18
8	**1**	B	PPh_3 + dpdcf	60	72 (55)	14	14
9	**2**	B	PPh_3	81	63 (52)	16	21
10	**2**	A	dppb	99	40	32	28
11	**2**	B	dppb	68	80 (72)	12	8
12	**3**	A	PPh_3	54	15	38	47
13	**3**	A	dppb	38	25	41	34
14	**3**	B	dppb	82	78 (70)	12	10
15	**4**	B	PPh_3	88	59	18	23
16	**4**	B	dppb	90	85 (75)	8	7
17	**5**	A	PPh_3	77	22	37	51
18	**5**	B	PPh_3	92	65 (54)	17	18
19	**5**	B	dppb	83	74 (68)	15	11

[a] Reaction conditions: 0.05 mmol $Pd(OAc)_2$, 0.1 mmol PPh_3 (or 0.05 mmol diphosphine); 14 ml toluene; 1.2 mmol $HSnBu_3$ (in 3 ml toluene), 50 °C, 1 bar CO.
[b] Method A: $HSnBu_3$ solution added in 10 min; method B: $HSnBu_3$ solution added in 2 h.
[c] Determined by GC.

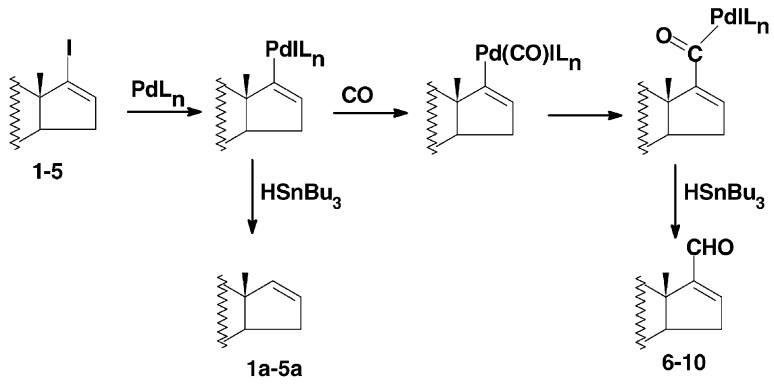

Fig. 3. A mechanistic representation of the elementary catalytic steps of formylation and hydrostannolysis resulting in **6**–**10** and **1a**–**5a**, respectively.

as substrates (80–85% olefinic products). Probably due to the presence of the NH group of the lactame (4-NH) and 6β-hydroxy functionalities tributyltin hydride acts mainly as a hydrodehalogenation agent. The application of flexible chelating phosphines like dppb and dppp proved to be superior both to rigid bidentate diphosphine (e.g. dpdcf = 1-diphenylphosphino-2,1′-[(1-dicyclohexylphosphino)-1,3-propanediyl]-ferrocene) and monodentate phosphine (PPh_3). The best conversions and selectivities, which enable facile isolation of the formyl products in good yields (70–75%), were obtained with palladium–dppb in situ systems.

As a summary, it can be stated that under appropriate reaction conditions conjugated unsaturated steroidal aldehydes (versatile intermediates of potential pharmacologically important derivatives) can be synthesized in yields of practical interest in palladium-catalyzed carbonylation reaction of easily available iodoalkenes as substrates. The reaction tolerates various functional groups on the A and B rings of the steroids.

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